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Time to therapeutic range (TtTR), anticoagulation control and cardiovascular events in vitamin K antagonists-naïve patients with atrial fibrillation.

Running title: Time to therapeutic range and atrial fibrillation

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ABSTRACT

BACKGROUND. Vitamin K antagonists (VKAs) reduce cardiovascular events (CVEs) in atrial fibrillation (AF) when a time in therapeutic range (TiTR) >70% is achieved. Factors affecting the time to achieve TR (TtTR) are unknown.

METHODS. Prospective observational study including 1406 non-valvular AF patients starting VKAs followed for a mean of 31.3 months (3690 patient/year); TiTR, TtTR and SAMe-TT_2R_2 score were calculated and CVEs were recorded.

RESULTS. Median TtTR was 8.0 days (IQR 5.0-18.0). Patients with high TtTR (i.e. >75th percentile) were more likely to be in AF than in sinus rhythm at entry (Odds ratio, OR:1.423, p=0.011).

Median TiTR was 60.0%; low TiTR (below median) was associated with SAMe-TT_2R_2 score (OR:1.175, p=0.001), high TtTR (>75th percentile, OR:1.357, p=0.017), and number of INR checks (OR:0.998, p=0.049). We recorded 113 CVEs (3.1%/year), with a higher rate seen in patients with TtTR >75th percentile compared to those below (log-rank test,p=0.006). A multivariable Cox regression analysis showed SAMe-TT_2R_2 score (HR: 1.331, p<0.001), TtTR >75th percentile (HR:1.505, p=0.047), TiTR <70% (HR:1.931, p=0.004), number of INR checks (HR:0.988, p<0.001), digoxin (HR:1.855, p=0.008), proton-pump inhibitors (HR:0.452, p<0.001), were independently associated with CVEs.

CONCLUSIONS. High TtTR is associated with poorer long-term quality of VKAs therapy. Patients with TtTR >18 days or with high SAMe-TT_2R_2 score should be considered for treatment with non-vitamin K oral anticoagulants.

Keywords: atrial fibrillation, vitamin k antagonists, TTR, cardiovascular events.

INTRODUCTION

Well-managed oral anticoagulation (OACs) with vitamin K antagonists (VKAs) is still a good therapeutic option for thrombo-prophylaxis in atrial fibrillation (AF) and remains widely used worldwide [1]. High-quality VKAs treatment reduces cerebrovascular and cardiac complications in AF populations when INR values are kept in a range of 2.0-3.0 and quality of OAC is maintained with a good 'time in therapeutic range' (TiTR) [2, 3]. Indeed, a TiTR>70% is associated with a low rate of cardiovascular events (CVEs) and bleeding complications[4, 5]. However, there is often some difficulty in achieving and maintain a good TiTR, and a high proportion (even up to 50%) of AF patients report poor-quality OAC with VKAs [6, 7].

To predict the quality of anticoagulation therapy in patients starting VKAs, the SAMe-TT_2R_2 score[8] has been developed and validated; this score includes Sex (female), Age (<60 years), medical history, Treatment (interacting drugs, e.g., amiodarone), Tobacco use (within 2-years), Race (non-white ethnicity)[9]. Patients with a SAMe-TT_2R_2 score >2 were shown to be more likely to have a lower TiTR during VKA therapy[9].

A particularly important period of OAC treatment is the inception phase, when dosage of VKAs for each patient is optimised, and patients are less confident with the management of a drug requiring a non-fixed daily dose. Previous studies have shown a lower quality of OAC in inception cohorts compared to patients on long-term OAC[10-12]. Moreover, high rates of discontinuation in warfarin naïve patients have also been reported[13].

In addition to TiTR, a significant parameter of anticoagulation quality is the 'Time to Therapeutic Range' (TtTR), which refers to the time needed to reach the therapeutic range after the administration of the first dose of VKAs. In clinical practice, the TtTR may be highly variable, with

some patients reaching the therapeutic range after the first few tablets of VKAs, and some taking several days or even weeks to achieve this.

The characteristics associated with high TtTR have been scarcely investigated[14], and it is unknown whether the initial TtTR may influence quality of TiTR and the rate of CVEs in a long-term follow of AF patients. The aim of our study was to investigate the relationship of TtTR to TiTR and CVEs in consecutive patients referring to an anticoagulation clinic for the prescription and management of VKAs therapy for non-valvular AF thromboprophylaxis.

METHODS

Analysis of TiTR and its determinants was a secondary endpoint of this prospective cohort study (clinicaltrials.gov NCT01882114). We included 2004 consecutive patients referring to the anticoagulation clinic of I Clinica Medica, Department of Internal Medicine and Medical Specialties of Sapienza University of Rome for the prescription and management of VKAs therapy for non-valvular AF thrombo-prophylaxis. Of these, 585 patients were warfarin-experienced (defined as having at least 1 dose of VKAs at entry) and were excluded from this analysis. Thus, the study cohort included 1419 patients starting VKAs. Exclusion criteria were prosthetic mechanical heart valves, severe cognitive impairment, chronic infections, autoimmune systemic disease, active cancer and liver insufficiency.

No exclusion criteria with respect to anticoagulation prior to VKA starting was applied. Thus, both patients on low-molecular weight heparin (LMWH) or aspirin, or no treatment were included. The presence of cardiovascular risk factors was defined as previously described [15]. Initial management of VKAs therapy was performed according to international guidelines [16], and anticoagulation monitoring was done with a computerized clinical decision support system (PARMA program,

Instrumentation Laboratory SpA, Milan). In patients taking aspirin at study entry (and no other indication than AF) antiplatelet drug was stopped at first dose of VKAs, while bridging LMWH was stopped when an INR >2 was achieved.

In all patients, we calculated the TtTR, expressed as the number of days needed to achieve the therapeutic range since the first administration of VKAs tablet. The TiTR was calculated according to the method of linear interpolation described by Rosendaal et al.[17]. The SAMe-TT_2R_2 score was calculated according to its original derivation study by Apostolakis et al.[8]. We also registered the number of visits for INR measurement during follow-up.

Definitions and adjudication of CVEs have been previously described[18]. Thus, CVEs included fatal/non-fatal myocardial infarction (MI) and ischemic stroke, systemic embolism, cardiac revascularization (coronary stent placement or coronary artery bypass graft surgery), vascular death and transient ischemic attack (TIA). The data on CVEs were prospectively collected and only the first event was used for the survival analysis.

Statistical analysis

Categorical variables were reported as counts (percentage), continuous variables were expressed as mean ± standard deviation or median and interquartile range (IQR), as appropriate. Independence of categorical variables was tested with the $\chi 2$ test. The normal distribution of parameters was assessed by Kolmogorov–Smirnov test. Student unpaired t test was used to compare means.

To investigate factors associated with high TtTR, we performed a multivariable logistic regression analysis using >75th percentile of TtTR as dependent variable. As covariates, we used the composite SAMe-TT_2R_2 score, and all other variables not included in this score, such as type of rhythm at entry (AF vs. sinus rhythm), digoxin, proton-pump inhibitors, allopurinol, antidepressant drugs, and

antiepileptic drugs. Afterward, a multivariable logistic regression analysis was carried out to assess adjusted odds ratio (OR) for variables affecting low TiTR (below median), using the same variables listed above with the addition of high TtTR (>75th percentile), and the number of INR checks during follow-up.

After dividing the AF population into two groups according to low or high (≤75th or >75th percentile, respectively) TtTR, the cumulative incidence of CVEs was estimated using a Kaplan–Meier product-limit estimator. Survival curves were formally compared using the log-rank test. Cox proportional hazards analysis was used to calculate the adjusted relative hazards of CVEs by each clinical variable. Only p values <0.05 were considered as statistically significant. All tests were two-tailed and analyses were performed using computer software packages (SPSS-20.0, SPSS Inc.).

All patients starting anticoagulation provided a written informed consent. The study protocol was approved by the local ethical board of Sapienza-University of Rome and was conducted according to principles of the Declaration of Helsinki. No extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study, all study analyses and drafting and editing of the paper.

RESULTS

TtTR and TiTR

Mean age of patients was 73.4±9.2 years and 41.5% were women (table 1); 70.9% were started on warfarin, and 29.1% on acenocumarol, at physician discretion. Median TtTR was 8.0 days (IQR 5.0-18.0). Characteristics of patients divided into those with high or low TtTR (i.e. ≤75th or >75th percentile) are reported in table 1; 23.5% of AF patients needed >18 days (75th percentile) to achieve therapeutic range. The two groups were similar for all clinical characteristics, but patients with higher TtTR were more likely to be in AF than in sinus rhythm at entry. A multivariable

logistic regression analysis (table 2) confirmed this association (OR: 1.423, 95%CI 1.084-1.869, p=0.011).

Patients were followed for a mean of 31.3±22.0 months (3690 patient/year), with no significant difference between patients with low or high TtTR (p=0.138). Median TiTR was 60.0% (IQR 47.0-73.0); patients with TtTR >75th percentile had significantly lower TiTR than those with low TtTR, spending most of time below TTR (Table 1).

When we investigated factors associated with low TiTR (table 3), we found that SAMe-TT_2R_2 score (OR: 1.175, p=0.001), high TtTR (75th percentile, OR: 1.357, p=0.017), and number of INR checks (OR: 0.998, p=0.049) were associated with low TiTR.

In particular, the number of patients with TiTR <70% increased according to the SAMe-TT_2R_2 score (from 56.7% for score=0, to 83.3% for a score=5, p=0.005).

Cardiovascular events

During follow-up, 13 patients were lost for survival analysis and 113 CVEs were recorded (3.1%/year) as follows: 13 fatal/non-fatal ischemic strokes, 10 TIAs, 27 fatal/non-fatal MIs, 25 cardiac revascularizations, 2 systemic embolisms and 36 cardiovascular deaths.

Patients with CVEs had higher SAMe-TT_2R_2 score (p=0.001), CHA_2DS_2-VASc score (p<0.001), and were more likely to have high TtTR (>75th percentile; 22.8 *vs.* 32.5%, p=0.028) and low TiTR <70% (67.4 *vs.* 76.5%, p=0.026) compared to those free from events. A higher rate of CVEs was found in patients with TtTR >75th percentile compared to those below (log-rank test p=0.006, figure 1).

On univariate Cox regression analysis, as compared to the 25th percentile of TtTR, the 50th percentile was not significantly associated with CVEs (HR: 1.108, 95% CI 0.665-1.847, p=0.693); while the 75th percentile was significantly associated with CVEs (HR:1.857, 95%CI 1.078-3.201, p=0.026).

A multivariable Cox regression analysis (table 4) found that SAMe-TT_2R_2 score (HR: 1.331, p<0.001), TtTR >75th percentile (HR:1.505, p=0.047), TiTR <70% (HR:1.931, p=0.004), number of INR checks (HR:0.988, p<0.001), digoxin (HR:1.855, p=0.008), proton-pump inhibitors (HR:0.452, p<0.001), were independently associated with CVEs.

DISCUSSION

In this prospective study of AF patients starting VKAs therapy in an anticoagulation clinic, we found that TtTR is an important predictor for the quality of anticoagulation, as reflected by TiTR. Second, patients with a longer TtTR were at increased risk for CVEs.

The TtTR has only been previously analysed in an ancillary analysis of the Edoxaban Versus Enoxaparin–Warfarin in Patients Undergoing Cardioversion of Atrial Fibrillation (ENSURE-AF) study [14]. This trial included 2,199 patients undergoing electrical cardioversion for AF, randomized to enoxaparin or warfarin (n=1104). The authors found a very similar median TtTR (7 days) and a modest association of renal function, while no other variables were found to be significantly associated to TtTR. Of note, the time of observation was significantly shorter than our study, as patients were only followed for 28 days on the study drug and 30 days after cardioversion[14].

In our study, being in AF at inception of OAC, compared to sinus rhythm, was a significant risk factor for high TtTR. A novel finding of our study is that high TtTR is an independent predictor of low TiTR, suggesting that the initial OAC management as a critical factor for future quality of OAC. This result was confirmed even after adjustment for SAMe-TT_2R_2 score that is a known predictor of TiTR[8, 19-21].

In addition, the number of INR checks was inversely associated to TiTR, meaning that a more careful management of OAC would result in a better-quality control and in a lower incidence of CVEs. Our findings therefore reinforce the evidence that TiTR is an important prognostic determinant in VKAs-treated AF patients [2, 3, 22], and that the SAMe-TT_2R_2 score has a significant association with CVEs[23]. This association is not surprising given that many variables included in this score and that affect TTR, are also associated with CVEs (i.e. smoking and cardiovascular risk factors).

A novel finding of our study is the association between proton pump inhibitors (PPI) and CVEs. Thus, while PPI seem not to influence TiTR[24], their use is inversely associated with the incidence of CVEs. The use of PPI in patients with cardiovascular disease on antithrombotic treatment is matter of debate[24, 25]. However, no study examining this association in patients with AF has been reported thus far. It should be considered that gastroesophageal reflux disease may represent a trigger for AF, and that some studies have demonstrated that acid suppressive therapy by PPI may help ameliorate symptoms associated with AF as well as facilitate conversion to normal sinus rhythm[26]. This could result into a benefit on CVEs in AF patients. However, we do not know if this could be regarded to as a class effect, or if rather there are differences among PPIs, which deserves further investigation. We also confirm our previous observation of an independent association between digoxin use and cardiovascular outcomes in patients with AF[18]. However, this association is still unresolved given the lack of randomized trial specifically including only AF patients.

Our findings have clinical implications. The first is that while high-risk AF patients, such as those who have already experienced a stroke, are usually kept under low-molecular weight heparin until a stable anticoagulation is reached, most are started directly on VKAs without any bridging therapy. Indeed, it is necessary for them to shorten the TtTR as much as possible, considering that the first 30 days of VKAs therapy has been associated with an increased risk of ischemic stroke in VKAs initiators compared to VKA-experienced patients[27].

The fact that we found only one significant predictor of TtTR suggests that other variables not considered in the present study may affect TtTR. This may include social and behavioural factors, such as adequate counselling of patients about the importance and the management of OAC with VKAs, awareness of the disease, family support, and changes in the perception of quality of life after OAC starting. Educational patient-tailored intervention was shown to improve TiTR in the

first 6 months of OAC[28, 29], and it might improve also TtTR. Thus, an educational study aimed to explore this issue is needed. A pharmacogenetic-guided strategy to predict optimal warfarin dosing has also been proposed to guide initial management of AF patients[30]. This approach was found to be effective as dose-finding for VKAs, but failed to reduce the number of INRs out of range[30, 31]. Concomitant use of daily low-dose oral vitamin K has also been suggested, with a non-significant effect on TiTR[32].

Finally, our findings may help clinicians in the management of AF patients starting OAC. Indeed, patients with high TtTR should be switched to non-vitamin K antagonist oral anticoagulants (also referred to as direct oral anticoagulants, DOACs), given that these agents perform better in AF patients with low TiTR [33]. Previous studies showed that the use of DOACs is associated with a higher adherence and persistence on OAC than VKAs. Thus, 12,307 AF patients starting VKA and 914 starting DOAC (apixaban, dabigatran, rivaroxaban), the persistence for those with $CHA_2DS_2VASc \geq 2$ was significantly higher for DOAC (83.0%) than VKA (65.3%, $p < 0.0001$) at one year [34]. Similarly, in 1745 matched pairs of patients starting warfarin or dabigatran, persistence rates were higher for dabigatran than for warfarin at both 6 months (72% vs. 53%) and 1 year (63% vs. 39%)[35]. Finally, in 7265 patients from primary care with newly diagnosed AF, after 360 days of treatment, persistence was 53.1% for rivaroxaban, 47.3% for dabigatran, and 25.5% for VKAs ($p < 0.001$ for rivaroxaban and dabigatran vs. VKA)[36].

Nevertheless, the limitations of our study pertain to its observational design and on the inclusion of only Caucasian patients. Whilst management of patients was performed according to European guidelines, the study was based in a single anticoagulation clinic which may limit generalisability to the wider population.

In conclusion, patients with high TtTR is associated with poorer long-term quality of VKAs therapy. Thus, patients with TtTR >18 days or with high SAMe-TT_2R_2 score should be considered for treatment with DOACs.

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Contribution of Authors

Daniele Pastori: study conception and design, analysis and interpretation of data, drafting and final approval of the manuscript, guarantor of the paper, taking responsibility for the integrity of the work as a whole.

Pasquale Pignatelli: interpretation of data, drafting and final approval of the manuscript;

Francesco Cribari: data collection, drafting and final approval of the manuscript;

Roberto Carnevale: data collection, drafting and final approval of the manuscript;

Mirella Saliola: data collection, drafting and final approval of the manuscript;

Francesco Violi: interpretation of data, drafting and final approval of the manuscript;

Gregory Y.H. Lip: study conception and design, interpretation of data, guarantor of the paper, taking responsibility for the integrity of the work as a whole, drafting and final approval of the manuscript.

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Figure Legends

Figure 1. Kaplan-Meier curves estimate of survival free from cardiovascular events according to values of TtTR (grey line ≤75th percentile; black line >75th percentile).

Table 1. Characteristics of study population.

	Overall (n=1406)	Low TtTR (≤75th percentile, n=1075)	High TtTR (>75th percentile, n=331)	p value
Age (years)	73.4±9.2	73.5±9.2	73.1±9.0	0.445
AF (*vs.* sinus rhythm)	64.7	62.9	70.4	0.013
Women (%)	41.5	41.1	42.9	0.567
Warfarin (vs. acenocumarol)	70.9	70.6	71.9	0.781
TiTR (%)	60.0 (47.0-73.0)	62.0 (47.0-74.0)	56.0 (45.0-71.0)	0.003
Low TiTR (%, below median, <60%)	47.4	45.1	54.8	0.002
Time below TR (%)	26.5±19.4	25.4±18.6	29.8±21.6	0.001
Time above TR (%)	14.2±12.9	14.3±13.0	13.9±12.6	0.645
Number of INR checks	72.5±47.1	74.4±47.3	66.8±46.0	0.010
CHA_2DS_2-VASc score	3.1 ±1.4	3.9±1.4	3.0±1.4	0.657
SAMe-TT_2R_2 score	1.6±1.0	1.6±1.0	1.6±1.1	0.892
HAS-BLED score	2.47±0.92	2.44±0.91	2.54±0.94	0.095
eGFR <60 ml/min (%)	33.0	33.1	32.5	0.934
Hypertension (%)	86.8	86.8	87.0	0.918
Diabetes mellitus (%)	21.5	21.1	22.7	0.541
History of cardiac events (%)	17.2	16.8	18.4	0.505
Heart failure (%)	12.0	11.2	14.5	0.121
History of cerebrovascular events (%)	14.2	15.0	11.8	0.151
Smoking (%)	13.4	13.3	13.8	0.848
Pulmonary disease (%)	14.3	13.7	16.4	0.243
Antiplatelet drugs (%)	10.8	10.0	13.3	0.105
Amiodarone (%)	15.5	14.6	18.4	0.099
Allopurinol (%)	7.1	7.2	6.9	0.895
Proton-pump inhibitors (%)	40.5	39.4	44.1	0.141
Digoxin (%)	14.2	14.2	13.9	0.928
Antidepressant drugs (%)	9.4	9.5	9.1	0.914
Antiepileptic drugs (%)	2.4	2.1	3.3	0.222
Statins (%)	36.9	36.8	37.2	0.948

AF: atrial fibrillation; INR: international normalized ratio; TTR: time in therapeutic range; TtTR: time to therapeutic range.

Table 2. Logistic regression analysis of factors associated to high TtTR >75th percentile.

	p value	OR	95% CI for OR	
			Lower	Upper
AF *vs.* sinus rhythm	0.011	1.423	1.084	1.869
SAMe-TT_2R_2 score	0.900	1.007	0.898	1.130
Digoxin	0.527	0.890	0.619	1.278
Proton-pump inhibitors	0.105	1.233	0.957	1.587
Allopurinol	0.822	0.946	0.581	1.539
Antidepressant drugs	0.688	0.914	0.589	1.418
Antiepileptic drugs	0.316	1.462	0.695	3.076

AF: atrial fibrillation; CI: confidence interval; OR: odds ratio.

Table 3. Linear regression analysis of factors associated with low TiTR (below median <60%)

	p value	OR	95% CI
SAMe-TT_2R_2 score	0.001	1.175	1.064-1.298
High TtTR (>75th percentile)	0.017	1.357	1.056-1.745
AF *vs.* sinus rhythm	0.124	1.197	0.952-1.505
Number of INR checks	0.049	0.998	0.995-1.000
Digoxin	0.141	1.265	0.925-1.728
Proton-pump inhibitors	0.206	1.152	0.925-1.434
Allopurinol	0.795	0.946	0.624-1.434
Antidepressant drugs	0.446	0.865	0.596-1.256
Antiepileptic drugs	0.228	1.555	0.759-3.184

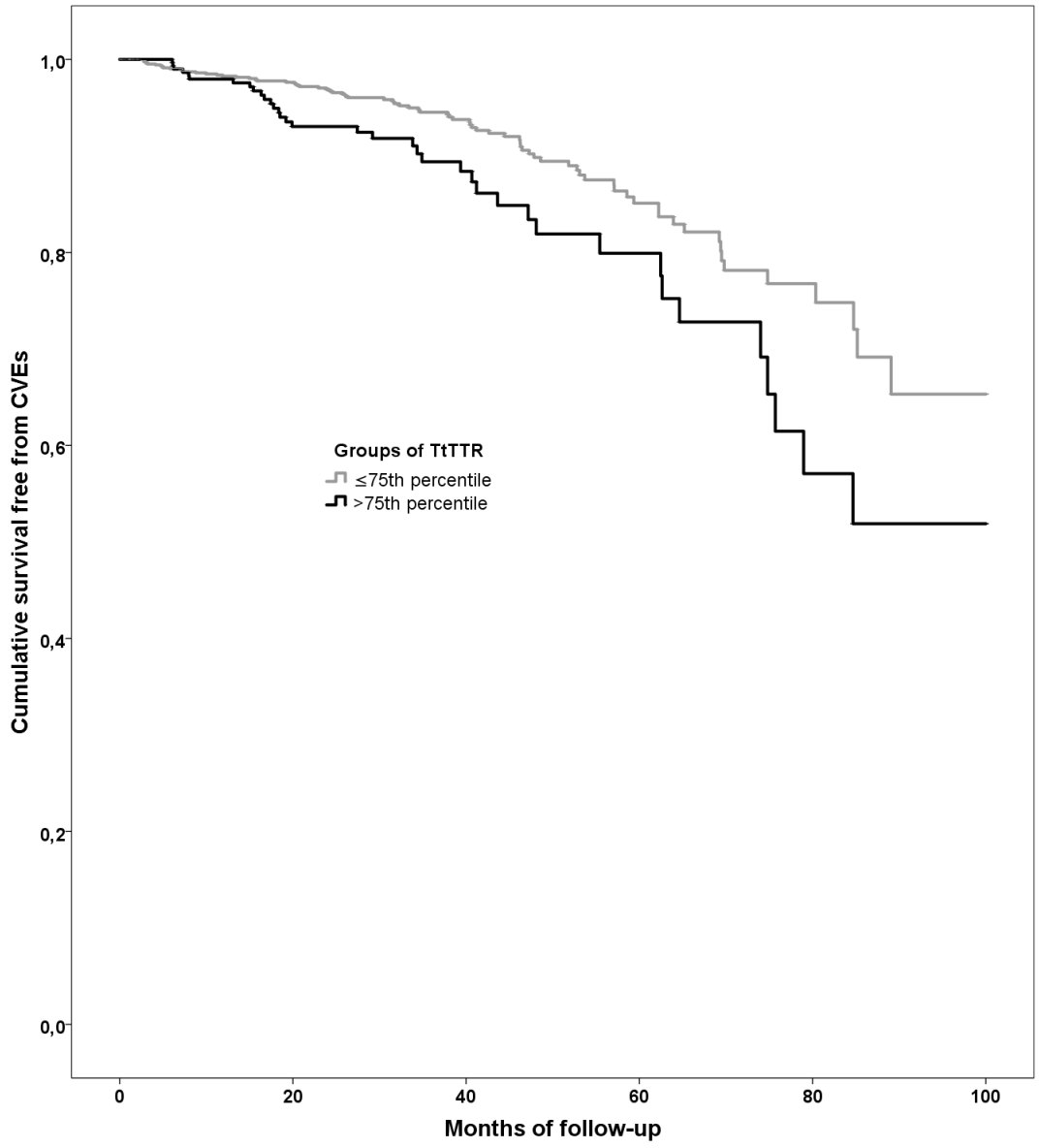
AF: atrial fibrillation; CI: confidence interval; OR: odds ratio; TTR: time in therapeutic range; TtTR: time to therapeutic range.

Table 4. Multivariable Cox Regression analysis of risk factors for cardiovascular events.

	p value	HR	95% CI for HR	
			Lower	Upper
SAMe-TT_2R_2 score	**<0.001**	**1.331**	**1.142**	**1.553**
High TtTR (>75th percentile)	**0.047**	**1.505**	**1.005**	**2.251**
TiTR <70%	**0.004**	**1.931**	**1.241**	**3.006**
AF *vs.* sinus rhythm	**0.490**	**0.866**	**0.575**	**1.304**
Number of INR checks	**<0.001**	**0.988**	**0.984**	**0.992**
Digoxin	**0.008**	**1.855**	**1.172**	**2.935**
Proton-pump inhibitors	**<0.001**	**0.452**	**0.296**	**0.690**
Allopurinol	**0.575**	**1.231**	**0.595**	**2.551**
Antidepressant drugs	**0.167**	**0.551**	**0.236**	**1.284**
Antiepileptic drugs	**0.456**	**0.579**	**0.138**	**2.433**

CI: confidence interval; HR: hazard ratio; **TiTR: time in therapeutic range**; TtTR: time to therapeutic range.

Figure 1.



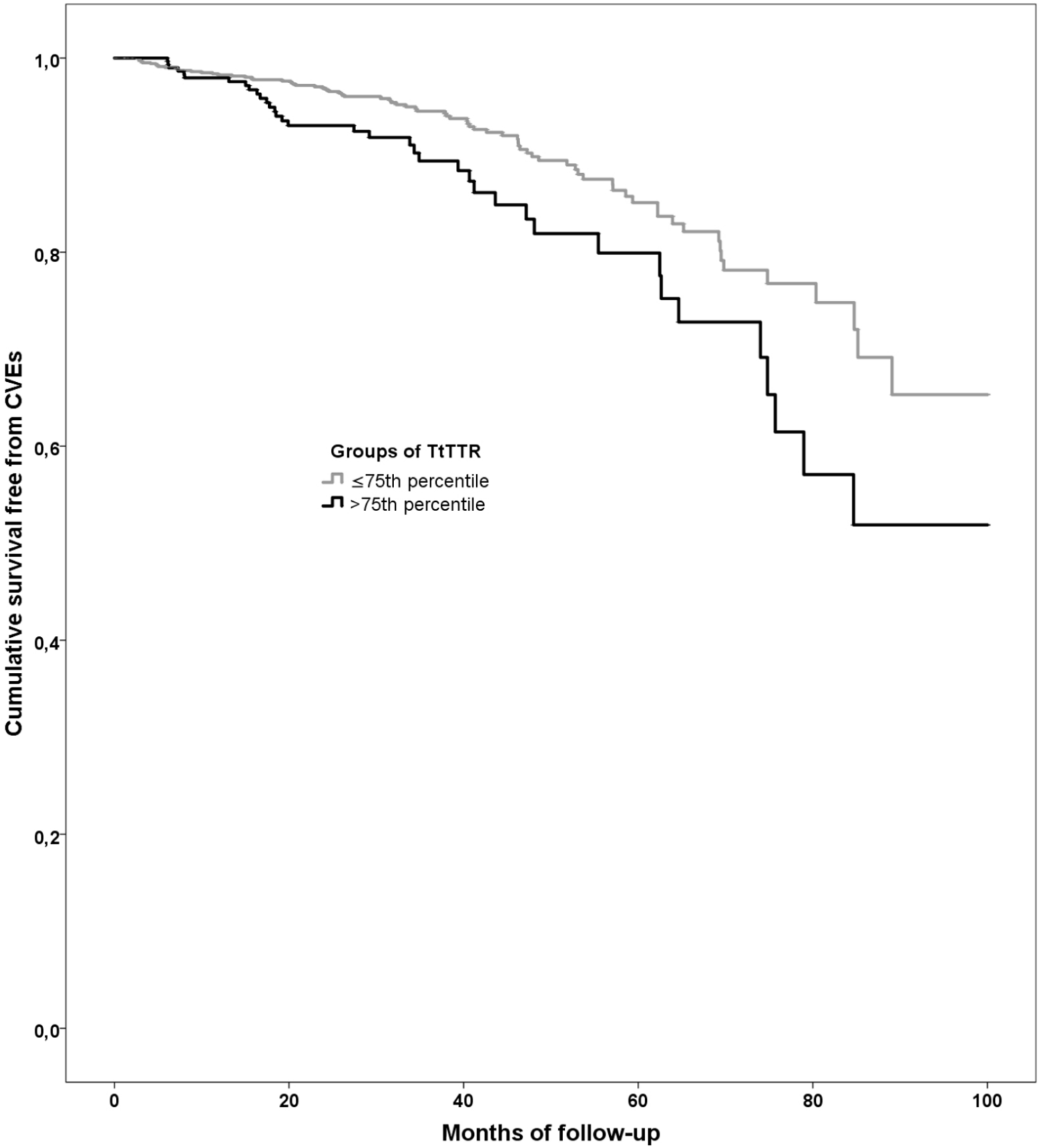

1,0
0,8
0,6
0,4
0,2
0,0
Cumulative survival free from CVEs
Groups of TtTTR
≤75th percentile
>75th percentile
0
20
40
60
80
100
Months of follow-up

Figure 1